sleep medicine, not a single function of sleep has been convincingly identified.

Sleep and synaptic homeostasis

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Abstract: We propose that sleep is linked to synaptic homeostasis. Specifically, we propose that: (1) Wakefulness is associated with synaptic potentiation in cortical circuits; (2) synaptic potentiation is tied to the homeostatic regulation of slow wave activity; (3) slow wave activity is associated with synaptic downscaling; and (4) synaptic downscaling is tied to several beneficial effects of sleep, including performance enhancement.

Walker presents strong evidence that sleep enhances certain memories, although it is not clear how it would do so. We have hypothesized that sleep promotes synaptic homeostasis: the maintenance of a baseline amount of synaptic weight impinging on neurons (Tononi & Cirelli 2003). One of the predictions of the hypothesis is that, under certain circumstances, synaptic homeostasis during sleep should lead to an increased signal-to-noise ratio (SNR) in cortical circuits, which should become apparent as enhanced performance. The hypothesis considers performance enhancing as one among several benefits of sleep and its homeostatic regulation. The hypothesis makes four claims:

1. Wakefulness is associated with synaptic potentiation. During wakefulness many brain circuits undergo LTP, resulting in a net increase in the strength or number of synaptic connections between neurons. Among supporting arguments are: (1) The expression of LTP-related genes, such as *Arc, BDNF, NGFI-A*, and phosphorylated CREB, is high during wakefulness and low during sleep (Cirelli et al. 1996; 2004a). (2) The activity of the noradrenergic system, which is responsible for the induction of LTP-related genes (Cirelli & Tononi 2000a; 2004), is high during wakefulness during salient events but is very low during sleep (Aston-Jones & Bloom 1981). (3) Absolute values of cerebral glucose consumption at rest are 18% higher after having been awake than after a night of sleep (Braun et al. 1997). Assuming that neural activity at rest is similar before and after sleep, such marked increase in baseline energy consumption suggests a diffuse increase in synaptic strength because close to 80% of brain metabolism is due to synaptic activity (Attwell & Laughlin 2001; Rothman et al. 2003). (4) From an evolutionary perspective, it makes sense that the potentiation of neural circuits should occur during wakefulness, when an animal is active and exposed to the environment, and not during sleep, when neural activity is unrelated to external events (Tononi & Cirelli 2001). Note that, according to the hypothesis, LTP-like changes in the brain occur whenever presynaptic firing is accompanied by postsynaptic depolarization in the presence of appropriate neuromodulators, whether or not an animal is engaged in learning paradigms.

2. Synaptic potentiation is tied to the homeostatic regulation of slow wave activity. One of the best-established facts in sleep regulation in mammals is that slow wave activity (SWA) increases in proportion to the duration of wakefulness and decreases progressively during sleep (Borbely 2001). The hypothesis states that increases in sleep SWA are a direct reflection of synaptic potentiation in cortical circuits during wakefulness. Among supporting arguments are: (1) Animals with a lesioned noradrenergic system, which have a greatly reduced expression of LTP-related molecules after wakefulness (Cirelli & Tononi 2000a; 2004), show a corresponding reduction in SWA homeostasis (Cirelli et al. 2004b). (2) Performing a visuomotor learning task produces an increase in SWA during subsequent sleep that is localized to right parietal cortical areas (Huber et al. 2004) presumably modified by learning (Ghilardi et al. 2000). (3) Sleep slow oscillations depend on cortico-cortical connections (Steriade 2003) and, according to computer simulations (Hill & Tononi 2005), their amplitude and synchronization reflects the overall strength of cortico-cortical synapses. Also, after visual deprivation during the critical period, which is associated with synaptic depression (Heynen et al. 2003), slow waves are reduced by 40% (Miyamoto et al. 2003). (4) The increase in power after wakefulness extends to other frequency bands (Cajochen et al. 1995), consistent with a generalized increase in neural synchronization due to increased synaptic strength.

3. Slow wave activity is associated with synaptic downscaling. According to the hypothesis, sleep SWA actively promotes a generalized depression or downscaling of synapses in response to the diffuse potentiation occurring during wakefulness. The progressive decrease of SWA during sleep reflects the progressive return of total synaptic weight to a baseline level. Among supporting arguments are: (1) During non-REM sleep, virtually all cortical neurons undergo a slow oscillation, cycling from a depolarized state of intense firing to a hyperpolarized state of silence at around 1Hz (Steriade 2003). Notably, sequences of spiking-hyperpolarization at around 1Hz are ideal for inducing synaptic depression (Kemp & Bashir 2001). (2) Recent molecular studies have shown that molecules implicated in synaptic depression are selectively upregulated during sleep (Cirelli et al. 2004a). (3) Studies in kittens show that sleep results in ocular dominance changes similar to those induced by monocular visual deprivation (Frank et al. 2001), which is known to act through LTD of cortical connections (Heynen et al. 2003). (4) Synaptic scaling occurs *in vitro* and *in vivo* in neocortical cells (Desai et al. 2002; Turrigiano 1999) and it can serve to preserve a constant level of synaptic input without obliterating memory traces (Miller & MacKay 1994). Note that downscaling is conceptually different from LTD, which affects select groups of synapses, or depotentiation, which affects only recently potentiated ones (Kemp & Bashir 2001). Note also that downscaling during sleep could be self-limiting since, when synaptic weight has returned to a baseline level, the amplitude of slow oscillations would be reduced to the point of preventing further downscaling. Finally, note that this process would be problematic during wakefulness but ideally compatible with sleep, a state during which the brain is both spontaneously active and virtually disconnected from the environment.

4. Synaptic downscaling is tied to the beneficial effects of sleep on performance. The performance-enhancing effect of sleep described by Walker is explained, according to the hypothesis, by an increase in neuronal SNR due to synaptic downscaling. Take the sleep-related enhancement in the visuomotor learning task we studied with high-density EEG (Huber et al. 2004). During wakefulness, synapses contributing to correct movements become progressively more efficacious (signal), but it is likely that potentiation extends to other synapses contributing to erroneous movements (noise). During sleep, assuming a threshold below which synapses become ineffective, downscaling would ensure that synapses contributing to the noise, being on average weaker than those contributing to the signal, cease to interfere in the execution, and SNR would increase. Indeed, we found that performance enhancement after sleep was strongly correlated with the increase in SWA in brain areas involved in the task, and the strongest correlation was with the increase of SNR during learning.

It should be emphasized that, while the synaptic homeostasis hypothesis accounts nicely for sleep-mediated enhancements in the performance of certain learning tasks, this would be only one of the benefits of synaptic downscaling during sleep. For example, downscaling could promote synaptic competition, especially during development, and avoid saturation. Most importantly, it could prevent unwelcome imbalances at the cellular level, including metabolic overload resulting from synaptic overload (Cirelli et al. 2004a). Finally, the hypothesis suggests new roles for REM sleep, as either complementary to non-REM sleep or achieving similar effects with different means (Tononi & Cirelli 2003).

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